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REMARKS

Claims 1, 28, 35, 42, 48, 55 and 62-92 are pending in the subject application. Applicants have amended claims 67 and 89 to more particularly claim what applicants regard as the invention. Support for the amendment to claims 67 can be found, *inter alia*, at page 22, lines 30-31, page 24, lines 26-27, page 25, lines 15-24, page 33, lines 18-23 and page 40, lines 4-8. Applicants have canceled claims 1, 28, 35, 42, 48, 55, 62-66, 69 and 73-88. Accordingly, claims 67, 68, 70-72 and 89-92 will be pending and under examination upon entry of this Amendment

In view of the arguments set forth below, applicants maintain that the Examiner's rejections made in the April 14, 2005 Office Action have been overcome, and respectfully request that the Examiner reconsider and withdraw same.

Rejection under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 1, 67-75 and 79-91 under 35 U.S.C. §112, first paragraph, as allegedly not enabling any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims. Applicants understand this rejection to apply to pending claims 67, 68, 70-72 and 89-92.

Specifically, the Examiner conceded that the specification is enabling for determining whether fluoxetine, imipramine, desipramine, 8-OH-DPAT or haloperidol, administered for a period of several days, two weeks, one month or 5, 11 or 28

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days can increase the amount of bromodeoxyuridine (BrdU) incorporated into cells or Ki-67 mRNA in cells after a suitable period of time, wherein the period of time is 24 hours and wherein the cells are a subset of cells of any type that are dividing. However, the Examiner stated that the specification does not reasonably provide enablement for administration of other compounds, for other non-specified amounts of time, use of agents other than BrdU or Ki-67 as markers of cell division, or other steps of determining if the agent increases cell division, or for determining if a specific type of cell is dividing, or waiting for other non-specified periods of time before animal sacrifice.

Initially, applicants note that the pending claims, as amended, recite specific durations of time and specific markers of cell division, thereby obviating the rejection with respect to those grounds.

In response to the Examiner's remaining grounds for rejection, applicants respectfully traverse for the reasons set forth below.

The test for enablement is whether one skilled in the art could, at the time of the invention, make and use the claimed invention based on the disclosure and information known in the art without undue experimentation. Applicants maintain that the claimed invention satisfies the test for enablement, and that the Examiner has not set forth sufficient grounds for concluding otherwise.

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The Examiner stated that the instant claims are not enabled for determining whether any agent can increase brain progenitor cell division because the specification only discloses methods involving fluoxetine, imipramine, desipramine, 8-OH-DPAT, or haloperidol.

In response, applicants note that the pending claims, as amended, are directed to the administration of specific classes of neuroactive agents. Applicants note that as a matter of law, an applicant does not have to enable every embodiment of a claim if it is shown that the vast majority of claims are enabled. The Examiner has conceded that the specification is enabled for fluoxetine, imipramine, desipramine and 8-OH-DPAT, i.e. neuroactive agents.

Applicants direct the Examiner's attention to the opinion of the court in U.S. v. Telecommunications Inc., 8 U.S.P.Q.2d 1217, 1222, 1223 (Fed. Cir. 1998), wherein the court held that "[s]ince one embodiment is admittedly disclosed in the specification, along with the general manner in which its current range was ascertained, we are convinced that other permutations of the invention could be practiced by those skilled in the art without undue experimentation. See SRI Int'l v. Matusushita Elec. Corp of America, 227 U.S.P.Q. 577, 586 (Fed. Cir. 1985) (the law does not require an applicant to describe in his specification every conceivable embodiment of the invention); Hybritech Inc., 231 U.S.P.Q. at 94 (the enablement requirement may be satisfied even though some experimentation is required)." Following the reasoning adopted by the court in U.S. v. Telecommunications, applicants maintain that because the application is enabled for at least

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four embodiments of neuroactive agents, i.e. fluoxetine, imipramine, desipramine and 8-OH-DPAT, one of skill in the art could practice the method using other classes of neuroactive agents, without undue experimentation. Therefore, applicants maintain that the instant claims are enabled for determining whether various classes of neuroactive agents can increase brain progenitor cell division.

The Examiner alleged that the instant claims are not enabled for observing changes in brain progenitor cell division because the specification does not provide sufficient guidance to allow a skilled artisan to conclude that any observed changes are actually in brain progenitor cells.

In response, applicants traverse. Applicants direct the Examiner's attention to, *inter alia*, page 40, lines 1-25 and Figures 2C and 2D which disclose bromodeoxyuridine-positive cells co-labeled with either the mature neuronal brain progenitor cell marker NeuN or the astroglial brain progenitor cell marker GFAP. Applicants maintain that these data confirm that increases in cell division were observed specifically in neural and glial brain progenitor cells and not merely in the broad genus of dividing cells or progenitor cells, as suggested by the Examiner. Therefore, applicants maintain that pending claims 67, 68, 70-72 and 89-92 satisfy the enablement requirement of 35 U.S.C. §112.

The Examiner also rejected claims 1, 67-75 and 79-91 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants understand this rejection to apply to pending claims 67, 68,

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70-72 and 89-92.

Specifically, the Examiner stated that the specification allegedly lacks adequate description for the claimed broad genus of agents which may increase brain progenitor cell division. In response, applicants again note that the pending claims, as amended, are directed only towards various classes of neuroactive agents for which representative examples are disclosed, i.e. fluoxetine, desipramine, imipramine and 8-OH-DPAT.

The Examiner also stated that the specification does not adequately describe the broad genus of brain progenitor cells. In response, applicants maintain that the specification provides representative examples of brain progenitor cells at, for example, page 40, lines 10-23, wherein neural brain progenitor cells and glial brain progenitor cells are disclosed.

Finally, the Examiner stated that the pending claims do not recite any time periods. In response, applicants note that the amended claims recite specific time periods.

Applicants maintain that pending claims 67, 68, 70-72 and 89-92 satisfy the written description requirement of 35 U.S.C. §112.

In view of the above remarks, applicants respectfully maintain that claims 67, 68, 70-72 and 89-92 satisfy the requirements of 35 U.S.C. §112, first paragraph.

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**Rejection under 35 U.S.C. §112, second paragraph**

The Examiner rejected claim 86 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

In response, applicants note that claim 86 has been canceled, rendering the rejection thereof moot.

**Rejections Under 35 U.S.C. §102**

The Examiner rejected claims 1, 67-75, 79, 85 and 87 under 35 U.S.C. §102(b) as allegedly anticipated by Yoshiumra et al. (PNAS USA 98:5874-5879) ("Yoshimura"). Applicants understand this rejection to apply to pending claims 67, 68, and 70-72.

Claim 67 provides a method for determining whether an agent increases brain progenitor cell division comprising the steps of (a) administering to a non-human subject for several days to one month an agent selected from the group consisting of tricyclics, selective serotonin reuptake inhibitors, selective norepinephrine uptake inhibitors, serotonin norepinephrine uptake inhibitors, alpha-2-adrenergic antagonists, growth factor receptor activators or modulators, NK1 antagonists, vasopressin V1B antagonists, mono-amino oxidase inhibitors, neuroleptics, antipsychotic inhibitors, GSK $\beta$ 3 inhibitors and agents that upregulate the sonic hedgehog pathway; (b) administering to the subject a compound which is a marker of cell division; (c) sacrificing the subject after 2 hours to 28 days; (d) quantitatively determining incorporation of the

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compound in the subject's brain tissue; and (e) comparing the amount so determined with the amount of compound in the brain tissue of a subject to which the agent was not administered wherein the agent's ability to increase brain progenitor cell division being indicated when the amount of compound in the brain tissue of the subject to which the agent was administered is greater than the amount of compound in the brain tissue of the subject to which the agent was not administered. Claims 68, 71 and 72 are dependent on claim 67.

In response to the Examiner's rejection, applicants respectfully traverse for the reasons set forth below.

Under 35 U.S.C. §102, and as stated in M.P.E.P. §2131.01, "[a] claim is anticipated only if *each and every element* as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." (emphasis added). Hence, to anticipate claims 67, 68, 71 and 72, Yoshimura would have to teach *each and every element* thereof. Yoshimura fails to do this.

Yoshimura teaches a method of determining whether *kainic acid* increases neurogenesis in adult hippocampus. Kainic acid is a natural marine product isolated from the red marine algae *D. simplex*. Yoshimura fails to teach that kainic acid is a member of any of the various classes of agents which are recited in claim 67 (i.e. tricyclics, selective serotonin reuptake inhibitors, selective norepinephrine uptake inhibitors, serotonin norepinephrine uptake inhibitors, alpha-2-adrenergic antagonists, growth factor receptor activators or modulators, NK1 antagonists, vasopressin V1B antagonists,

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mono-amino oxidase inhibitors, neuroleptics, antipsychotic inhibitors, GSK $\beta$ 3 inhibitors, or agents that upregulate the sonic hedgehog pathway) and the Examiner has failed to show otherwise. Furthermore, the method of Yoshimura comprises a single administration of kainic acid (p. 5874, right column), whereas claim 67 comprises administration of an agent for several days to one month. Therefore, Yoshimura fails to teach each and every element of claim 67. Dependent claims 68 and 70-72 are also not anticipated as they depend from claim 67.

The Examiner also rejected claims 1, 67, 68, 70-75, 79, 81-83 and 88 under 35 U.S.C. §102(b) as allegedly anticipated by Malberg et al (2000. J. Neurosci 20:9104-9110) ("Malberg"). Applicants understand this rejection to apply to pending claims 67, 68 and 70-72.

In response to the Examiner's rejection, applicants respectfully traverse for the reasons set forth below.

To anticipate claims 67, 68 70-72, Malberg would have to teach each and every element thereof. Malberg fails to do this.

Specifically, Malberg teaches a method for determining whether fluoxetine or haloperidol increase the number of bromodeoxyuridine-labeled cells in the dentate gyrus and hilus of the hippocampus. However, Malberg teaches the above method comprising the administration of bromodeoxyuridine before the administration of fluoxetine (See p. 9105, left column) whereas claim 67 comprises administering a marker of cell division after administration of the agent. Therefore, Malberg fails to teach each and every element of claim 67.

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Dependent claims 68 and 70-72 are also not anticipated as they depend from claim 67.

The Examiner further rejected claims 1, 67, 68, 70, 71, 73-75, 79, 84, 87 and 88 under 35 U.S.C. §102(a) as allegedly anticipated by Zhang et al (2002. Stroke 33:2675-2680). ("Zhang"). Applicants understand this rejection to apply to pending claims 67, 68 and 70-72.

In response to the Examiner's rejection, applicants respectfully traverse for the reasons set forth below.

To anticipate claims 67, 68 and 70-72, Zhang would have to teach each and every element thereof. Zhang fails to do this.

Specifically, Zhang teaches a method for determining whether sildenafil, a phosphodiesterase inhibitor, increases neurogenesis and promotes functional recovery after stroke in rats. Applicants note that phosphodiesterase inhibitors are not one of the classes of compounds which are recited by claim 67. Therefore, Zhang fails to teach each and every element of claim 67. Dependent claims 68 and 70-72 are also not anticipated as they depend from claim 67.

The Examiner further rejected claims 1, 67, 68, 70-75, 79, 85, and 87-91 as allegedly anticipated by Lai et al. (Proceedings of the Second Joint EMBS/BMES Conference. October 23-26, 2002, p. 743-744). ("Lai 2002"). Applicants understand this rejection to apply to pending claims 67, 68, 70-72 and 89-91.

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In response to the Examiner's rejection, applicants respectfully traverse for the reasons set forth below.

Claim 67 is discussed above. Claim 68, 70-72 and 89-91 are dependent on claim 67.

To anticipate claims 67, 68, 70-72 and 89-91, Lai 2002 would have to teach each and every element thereof. Lai 2002 fails to do this.

Specifically, Lai 2002 teaches a method for determining whether sonic hedgehog can regulate neural stem cell proliferation *in vitro* and *in vivo*. However, Lai 2002 teaches a single administration of a viral vector comprising sonic hedgehog cDNA, whereas claim 67 provides a method for determining whether an agent can increase brain progenitor cell division comprising administering the agent to a non-human subject for *several days to one month*. Therefore, Lai 2002 fails to teach each and every element of claim 67. Dependent claims 68, 70-72 and 89-91 are also not anticipated as they depend from claim 67.

The Examiner further rejected claims 1, 67-75, 79 and 85-91 as allegedly anticipated by Lai et al. (2003, *Nature Neuroscience* 6:21-27) ("Lai 2003"). Applicants understand this rejection to apply to pending claims 67, 68, 70-72 and 89-91.

In response to the Examiner's rejection, applicants respectfully traverse.

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To anticipate claims 67, 68, 70-72 and 89-91, Lai 2003 would have to teach each and every element thereof. Lai 2003 fails to do this.

Specifically, and like Lai 2002, Lai 2003 teaches a method for determining whether sonic hedgehog can regulate neural stem cell proliferation *in vitro* and *in vivo*. However, Lai 2003 teaches a *single* administration of either cDNA encoding sonic hedgehog or cyclodextrin, whereas claim 67 discloses a method for determining whether an agent can increase brain progenitor cell division comprising administering the agent to a non-human subject *for several days to one month*. Therefore, Lai 2003 fails to teach each and every element of claim 67. Dependent claims 68, 70-72 and 89-91 are also not anticipated as they depend from claim 67.

Finally, the Examiner rejected claims 1, 67-70, 73-74, 79, 86, 87 and 90 under 35 U.S.C. §102(b) as allegedly anticipated by Wallace (1999. *Current Biology* 9:445-448) ("Wallace"). Applicants understand this rejection to apply to pending claims 67, 68, 70 and 90.

In response to the Examiner's rejection, applicants respectfully traverse.

To anticipate claims 67, 68, 70 and 90, Wallace would have to teach each and every element thereof. Wallace fails to do this.

Specifically, Wallace teaches a method for determining whether hybridomas that *inhibit* the sonic hedgehog pathway can

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regulate granule neuron precursor cell proliferation in mice. Agents that inhibit sonic hedgehog pathway are not one of the classes of neuroactive agents recited by claim 67. Therefore, Wallace fails to teach each and every element of claim 67. Dependent claims 68, 70 and 90 are also not anticipated as they depend from claim 67.

In view of the above remarks, applicants maintain that claims 67, 68, 70-72 and 89-92 satisfy the requirements of 35 U.S.C. §102.

**Rejections Under 35 U.S.C. §103(a)**

The Examiner rejected claims 1, 67, 80, 85 and 87-92 under 35 U.S.C. §103(a) as allegedly obvious over Frank-Kamenetsky et al (2002. J. Biology 1:10.1-10.19) ("Frank-Kamenetsky") in view of Wallace. Applicants understand this rejection to apply to pending claims 67 and 89-92.

In response to the Examiner's rejection, applicants respectfully traverse for the reasons set forth below.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim. First, the cited references, when combined, must teach or suggest each element of the claim. Second, one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. And third, there would have been a reasonable expectation that the claimed invention would succeed. The Examiner has failed to do this.

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Specifically, applicants maintain that the cited references fail to support a *prima facie* case of obviousness because combined, they do not teach or suggest every element of the claimed invention.

Wallace is as described above.

Frank-Kamenetsky teaches the structure of three modulators of sonic hedgehog signaling, Hh-Ag 1.1, Hh-Ag 1.2 and Hh-Ag 1.3.

As discussed above, Wallace fails to teach or suggest each and every element of claim 67 because it only discloses methods comprising the administration of agents that *inhibit* the sonic hedgehog pathway, which are not one of the classes of neuroactive agents recited in claim 67.

Frank-Kamentesky fails to overcome the deficiencies of Wallace. Frank-Kamentesky discloses a method of determining whether Hh-Ag 1.1 increases neurogenesis *in vitro*. Frank-Kamentesky also fails to teach or suggest the administration of a *marker of cell division* after administration of the agent, as recited in step (b) of claim 67. Dependent claims 89-92 are also not obviated for these reasons. Thus, these two references, when combined, do not teach all elements of the claims, and thus fail to render those claims obvious.

The Examiner also rejected claims 1, 67 and 84 under 35 U.S.C. §103 as allegedly obvious over Fujii (1997. Cancer Causes and Control 8:524-528) ("Fujii") in view of Yoshiumura. Applicants understand this rejection to apply to pending claim 67.

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In response to the Examiner's rejection, applicants respectfully traverse for the reasons set forth below.

Applicants maintain that the cited references fail to support a *prima facie* case of obviousness because combined, they do not teach or suggest every element of the claimed invention.

Yoshimura is as described above.

Fujii teaches a method comprising administration of nimustine to pregnant rats and determination of a decrease in the frequency of kainic acid-induced wet dog shakes.

As discussed above, Yoshimura fails to teach or suggest each and every element of claim 67 because it only discloses methods involving the marine product kainic acid, which neither Yoshimura nor the Examiner have shown to be a member of any of the various classes of agents recited in claim 67. Furthermore, Yoshimura discloses a method comprising a *single* administration of kainic acid, whereas the method of claim 67 comprises administration of an agent for *several days to one month*.

Fujii fails to overcome the deficiencies of Yoshimura. Fujii teaches methods involving the anti-cancer agent nimustine and hypothesizes that the effects to nimustine are mediated by alterations in neurogenesis. Fujii fails to address the deficiencies of Yoshimura because Fujii, and the Examiner, have failed to show that nimustine is a member of any of the various classes of agents covered by claim 67. Thus, these two references, when combined, do not teach all elements of

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the rejected claims, and thus fail to render those claims obvious.

In view of the above remarks, applicants maintain that claims 67 and 89-92 satisfy the requirements of 35 U.S.C. §103.

**Summary**

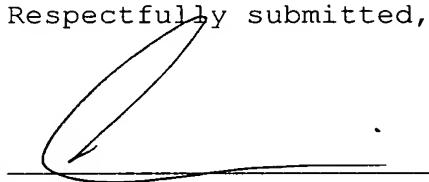
Applicants maintain that the claims pending are in condition for allowance. Accordingly, allowance is respectfully requested.

If a telephone conference would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

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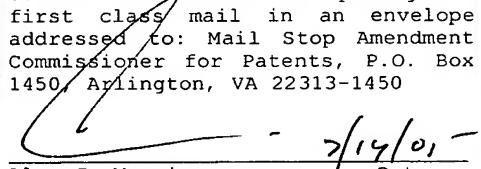
No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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